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(71) Applicants *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HANCOCK, Bruno [GB/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). WINTERS, Conrad [GB/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GERTZ, Barry [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GOTTESDIENER, Keith [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(54) Title: COMPOSITIONS FOR A ONCE A DAY TREATMENT OF CYCLOOXYGENASE-2 MEDIATED DISEASES

(57) Abstract

This invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said compositi n being suitable for once a day oral administration, said composition comprising 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone. The invention is also directed to a method of treating cyclooxygenase-2 mediated diseases comprising the once a day oral administration of 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone. The invention is also directed to the use of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a medicament containing 2.5 to 250 mgs of said compound for once a day administration for the treatment of cyclooxygenase-2 mediated diseases.

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TITLE OF THE INVENTION

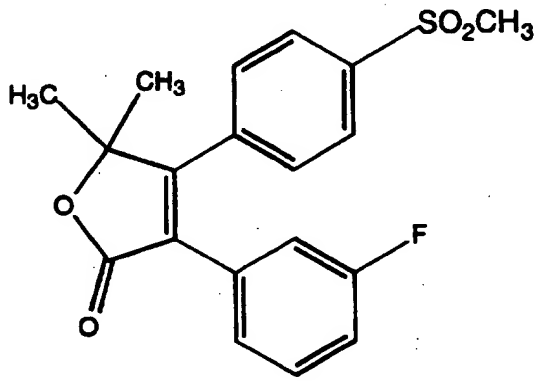
COMPOSITIONS FOR A ONCE A DAY TREATMENT OF CYCLOOXYGENASE-2 MEDIATED DISEASES

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions for the treatment of cyclooxygenase-2 mediated diseases, methods of treatment thereof and the use of a compound in the manufacture of a medicament.

In particular, this invention relates to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day administration, said composition comprising

5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl) phenyl)-2-(*5H*)-furanone.



Non-steroidal anti-inflammatory agents are normally administered 2 to 4 times daily. The relatively short half-life of most non-steroidal anti-inflammatory agents means that once a day administration is impractical and even twice a day administration is unusual. The relatively large doses needed to achieve once a day treatment of conventional non-steroidal anti-inflammatory agents would also lead to side effects so that there is a general understanding that once a day administration is unlikely to be achievable.

Surprisingly a compound has been identified which can be employed on a once a day basis and which will not produce an

unacceptable level of side effects on such a regimen, and in particular will not cause an unacceptable level of gastric side effects.

US 5,474,995, issued December 12, 1995, WO 95/00501, published January 5, 1995 and WO 95/18799, published July 13, 1995, disclose 3,4-di-substituted furanones and derivatives thereof as potent, selective inhibitors of cyclooxygenase-2. We have found that 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone, possesses a surprising combination of attributes that make it possible to formulate and use the composition in a surprising manner. Not only is the compound potent, safe and effective at modest oral dosages of 2.5 to 250 mg of agent per day, but in addition this active agent possesses a half-life in humans of sufficient length that a single oral dose of 2.5 to 250 mg of agent per day will provide effective safe anti-inflammatory treatment over a 24 hour period. Such active agents are particularly useful in the treatment of chronic indications, including arthritis, pain, Alzheimer's disease and the like.

SUMMARY OF THE INVENTION

This invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

The invention is also directed to a method of treating cyclooxygenase-2 mediated diseases comprising the once a day oral administration of 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

The invention is also directed to the use of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a medicament containing 2.5 to 250 mgs of said compound for once a day administration for the treatment of cyclooxygenase-2 mediated diseases.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone, and a pharmaceutical carrier therefor.

5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone, its utility and methods of making them are disclosed in US 5,474,995, issued December 12, 1995, WO 95/00501, published January 5, 1995 and WO 95/18799, published July 13, 1995, which are hereby incorporated by reference.

As discussed in US 5,474,995 compounds including 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. It is also useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer's Disease (ie Alzheimer's dementia).

The compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its potent inhibitory activity against cyclooxygenase-2 (COX-2) and/or its selectivity for inhibiting COX-2 over cyclooxygenase-1 (COX-1) the specified compound is also useful

as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such NSAIDS may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to surgery or taking anticoagulants; and those susceptible to NSAID induced asthma.

For the treatment of any of these cyclooxygenase mediated diseases the compound may be administered orally.

As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. The compositions are intended for oral use and may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc.

Other suitable formulations are set forth in U.S. Patent No. 5,474,995. However, in view of the unique set of properties possessed by 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone, including long half-life, low solubility, high potency and de minimis gastrointestinal (GI) side effects we have found the following oral formulations to be of particular value:

Rapidisc® – In view of the above mentioned characteristics, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone is particularly well suited for a rapid dissolving sublingual formulation. For example, due to the lack of GI side-effects, the agent need not be taken with a large amount of water. Suitable Rapidisc® formulations and methods of making same are disclosed in US 4,305,502, US 4,371,516, US 4,470,202, US 4,758,598, US 4,754,597, US 5,046,618 and US 5,188,882, all of which are hereby incorporated by reference.

As mentioned in the Background section, we have found 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone to possess a surprising combination of attributes. Not only are these active agents potent safe and effective at modest oral dosages of 2.5 to 250 mg of agent per day, but in addition these active agents possess a half-life in humans of sufficient length that a single oral dose of 2.5 to 250 mg of active agent per day will provide effective safe anti-inflammatory treatment over a 24 hour period. Such agents are particularly useful in the treatment of chronic indications, such as rheumatoid and osteo arthritis as well as Alzheimer's Disease.

Oral dosage levels for agents 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone are of the order of from about 2.5 to 250 mg per patient per day.

The amount of active agent that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from 2.5 to 250 mg of agent compounded with an appropriate and convenient amount of carrier material which may vary from about

5 to about 95 percent of the total composition. Dosage unit forms may typically contain 2.5, 5, 10, 12.5, 20, 25, 37.5, 50, 75, 100, 125, 150, 175 or 250 mg of active agent.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination and the type and severity of the particular disease undergoing therapy. For many patients, a dosage range of 2.5 to 125 or 10 to 75 mg per day is preferred.

For long term therapy, such as in the treatment of chronic diseases including rheumatoid arthritis, osteoarthritis or Alzheimer's disease, a dosage of 10 to 75 or 5 to 125 mg per day is preferred. More particularly, for the treatment of osteoarthritis, a dosage of 10, 25 or 50 mg per day is preferred, whereas for the treatment of rheumatoid arthritis, 25, 50 or 75 mg per day is preferred. For the treatment of non-chronic indications such as headache or post-operative swelling and pain, 5, 10, 25 or 50 mg per day is preferred.

Accordingly, in one aspect this invention is directed to a pharmaceutical composition for the treatment of COX-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising a 2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone, and a pharmaceutical carried therefor.

Within this aspect there is a first genus of compositions comprising 5, 10 or 25 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

Within this aspect there is a second genus of compositions comprising 10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

Within this genus there is a class of compositions comprising 10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

Within this genus there is a second class of compositions comprising 10, 25, or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

Within this genus there is a third class of compositions comprising 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

In another aspect the invention is directed to a unit dose oral form which comprises from 5 to 22.5 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone, for example, 12.5 or 20 mg.

EXAMPLE 1

Wet granulated tablet composition

Amount per tablet	Ingredient
25 mg	COX-2 Inhibitor
79.7 mg	Microcrystalline cellulose
79.7 mg	Lactose monohydrate
6 mg	Hydroxypropyl cellulose*
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accomodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

* Klucel®LF®from Aqualon

EXAMPLE 1a

Wet granulated tablet composition

Amount per tablet	Ingredient
12.5 mg	COX-2 Inhibitor
86 mg	Microcrystalline cellulose
86 mg	Lactose monohydrate

6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

EXAMPLE 1b

Wet granulated tablet composition

Amount per tablet	Ingredient
10 mg	COX-2 Inhibitor
87.2 mg	Microcrystalline cellulose
87.2 mg	Lactose monohydrate
6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

EXAMPLE 1c

Wet granulated tablet composition

Amount per tablet	Ingredient
5 mg	COX-2 Inhibitor
89.7 mg	Microcrystalline cellulose
89.7 mg	Lactose monohydrate
6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

EXAMPLE 2

Directly compressed tablet composition

Amount per tablet	Ingredient
25 mg	COX-2 Inhibitor
106.9 mg	Microcrystalline cellulose

106.9 mg	Lactose anhydrate
7.5 mg	Croscarmellose sodium
3.7 mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accomodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

EXAMPLE 2a

Directly compressed tablet composition

Amount per tablet	Ingredient
12.5 mg	COX-2 Inhibitor
113.2 mg	Microcrystalline cellulose
113.2 mg	Lactose anhydrate
7.5 mg	Croscarmellose sodium
3.7 mg	Magnesium stearate

EXAMPLE 2b

Directly compressed tablet composition

Amount per tablet	Ingredient
10 mg	COX-2 Inhibitor
42.5 mg	Microcrystalline cellulose
42.5 mg	Lactose anhydrate
4 mg	Croscarmellose sodium
1 mg	Magnesium stearate

EXAMPLE 2c

Directly compressed tablet composition

Amount per tablet	Ingredient
5 mg	COX-2 Inhibitor

45 mg	Microcrystalline cellulose
45 mg	Lactose anhydrate
4 mg	Croscarmellose sodium
1 mg	Magnesium stearate

EXAMPLE 3

Hard gelatin capsule composition

Amount per capsule	Ingredient
25 mg	COX-2 Inhibitor
37 mg	Microcrystalline cellulose
37 mg	Lactose anhydrate
1 capsule	Hard gelatin capsule
1 mg	Magnesium stearate

Capsule dose strengths of between 1 and 50 mg can be accomodated by varying total fill weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

EXAMPLE 4

Oral solution

Amount per 5 mL dose	Ingredient
50 mg	COX-2 Inhibitor
To 5 mL	with Polyethylene oxide 400

Solution dose strengths of between 1 and 50 mg/5mL can be accomodated by varying the ratio of the two ingredients.

EXAMPLE 5

Oral suspension

Amount per 5 mL dose	Ingredient

101 mg	COX-2 Inhibitor
150 mg	Polyvinylpyrrolidone
2.5 mg	Poly oxyethylene sorbitan monolaurate
10 mg	Benzoic acid

To 5 mL with sorbitol solution (70%)

Suspension dose strengths of between 1 and 50 mg/5mL can be accomodated by varying the ratio of the first and last ingredients.

EXAMPLE 6

Intravenous infusion

Amount per 200mL dose	Ingredient
1 mg	COX-2 inhibitor
0.2 mg	Polyethylene oxide 400
1.8 mg	Sodium chloride
to 200mL	Purified water

STARTING MATERIALS

5,5,-Dimethyl-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Step 1: Methyl 2-trimethylsilyloxyisobutyrate

To a solution of 1.2 mL (10.4 mmol) of methyl 2-hydroxy-isobutyrate in 50 mL of CH_2Cl_2 were added 1.2 g (17.6 mmol) of imidazole and 2.1 mL (16.6 mmol) of TMSCl. The mixture was stirred at r.t. for 1.5 h and quenched with 20 mL of H_2O. The organic layer was dried over $MgSO_4$, concentrated and passed through a short plug of silica gel eluted with 9:1 hexane/EtOAc. Evaporation of solvent afforded 1.27 g of the title compound as a colorless oil.
^1H NMR (CD_3COCD_3) δ 0.08 (9H, s), 1.38 (6H, s), 3.67 (3H, s).

Step 2: 2-Trimethylsilyloxy-4'-(methylthio)isobutyrophenone

A solution of 204 mg (1.0 mmol) of 4-bromothioanisole in 2.5 mL of THF was cooled to -78°C and treated with 0.42 mL of 2.5 M n-BuLi solution in hexane. After stirring at -78°C for 1 h, a solution of 380 mg (2.0 mmol) of methyl 2-trimethylsilyloxyisobutyrate (Step 1) in 2 mL of THF was added. The mixture was stirred at -78°C for 2 h and then quenched with NH_4OAc buffer. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 19:1 hexane/EtOAc to give 95 mg of the title product.

^1H NMR (CD_3COCD_3) δ 0.05 (9H, s), 1.52 (6H, s), 2.53 (3H, s), 7.33 (2H, d), 8.12 (2H, d).

Step 3: 2-Hydroxy-4'-(methylthio)isobutyrophenone

To a solution of 40 mg (0.14 mmol) of 2-trimethylsilyloxy-4'-(methylthio)isobutyrophenone (Step 2) in 2 mL THF was added 0.2 mL of 1 M n-Bu_4NF in THF. The resulting mixture was stirred for 30 min and then quenched with 10 mL of NH_4OAc buffer. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 4:1 hexane/EtOAc to give 25 mg of the title product.

^1H NMR (CD_3COCD_3) δ 1.50 (6H, s), 2.54 (3H, s), 4.68 (1H, s), 7.30 (2H, d), 8.15 (2H, d).

Step 4 2-hydroxy-4'-(methylsulfonyl)isobutyrophenone

To a solution of 2-hydroxy-4'-(methylthio)isobutyrophenone (Step 3) (45 g) in t-BuOH (500 mL) and CH_2Cl_2 (200 mL) was added a solution of OXONE™ (194 g) in H_2O (1.4 L). The reaction mixture was stirred for 18 h at r.t. and then extracted with EtOAc (3 x 500 mL). The organic extracts were combined and dried over Na_2SO_4 and the solvent was evaporated . The residue was swished in Et_2O/hexane to give the title compound as a yellow solid (47.4 g).

Step 5 3-Fluorophenylacetic acid, 1,1-dimethyl-2-(4-(methylsulfonyl)phenyl)-2-oxo-ethyl ester

A mixture of 2-hydroxy-4'-(methylsulfonyl)isobutyrophenone (Step 4) (100 g), 3-fluorophenylacetic acid (83 g), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (225 g) and DMAP (25 g) in CH_2Cl_2 (2 L) was mechanically stirred for 17 h at r.t.. A solution of 1N HCl (1 L) was then added and the organic phase was separated, washed with a saturated solution of Na_2CO_3 (0.4 L) and dried over MgSO4. After concentration, the residue was purified by silica gel chromatography, eluting with 30% EtOAc/hexane to give the title compound as a white solid (133 g).

Step 6 5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl))-2-(5*H*)-furanone

A solution of the product from Step 5 (120 g) in CH_2Cl_2 (1 L) was treated with DBU (81.6 g) and stirred for 1 h at r.t.. The reaction mixture was then treated with 1N HCl (550 mL) and the organic phase was separated, washed with saturated $NaHCO_3$ and dried over MgSO4. After concentration, the crude was swished with 20% EtOAc/hexane (450 mL), and filtered to give the title compound as a white solid (108.4 g, m.p. 172.7°C).

Analysis	Calculated	C 63.32; H 4.75
	Found:	C 63.50; H 4.79

ABBREVIATIONS

DBU	= 1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	= 4-(dimethylamino)pyridine
OXONE™	= $2KHSO_5.KHSO_4.K_2SO_4$
THF	= tetrahydrofuran
TLMSCl	= trimethylsilyl chloride

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 2.5 to 250 mg of a compound is 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

2. A composition according to Claim 1 comprising 5, 10 or 25 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(*5H*)-furanone.

3. A composition according to Claim 1 comprising 10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(*5H*)-furanone.

4. A composition according to Claim 1 comprising 10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(*5H*)-furanone.

5. A composition according to Claim 1 comprising 10, 25, or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(*5H*)-furanone.

6. A composition according to Claim 1 comprising 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(*5H*)-furanone.

7. A pharmaceutical composition according to Claim 1, 2, 3, 4, 5, or 6 further comprising

(a) Microcrystalline cellulose,
(b) Lactose monohydrate,
(c) Hydroxypropyl cellulose,
(d) Croscarmellose sodium, and
(e) Magnesium stearate; or further comprising

(a) Microcrystalline cellulose,
(b) Lactose anhydrate,
(c) Croscarmellose sodium, and
(d) Magnesium stearate; or further comprising

Polyethylene oxide 400; or further comprising

(a) Sorbitol solution,
(b) Polyvinylpyrrolidone,
(c) Poly oxyethylene sorbitan monolaurate, and
(d) Benzoic acid.

8. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:
administration orally once a day to a patient in need of such treatment 2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

9. A method according to Claim 8 comprising:
administration orally once a day to a patient in need of such treatment 5, 10 or 25 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

10. A method according to Claim 8 comprising:
administration orally once a day to a patient in need of such treatment 10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

11. A method according to Claim 8 comprising:
administration orally once a day to a patient in need of such treatment 10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(*5H*)-furanone.

12. A method according to Claim 8 comprising:

administration orally once a day to a patient in need of such treatment 10, 25 or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

13. A method according to Claim 8 comprising:
administration orally once a day to a patient in need of such treatment 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

14. A method of treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent comprising:
administration orally once a day to a patient in need of such treatment a composition according to Claim 7.

15. A method according to Claim 9 for the treatment of non-chronic headache, pain or swelling.

16. A method according to Claim 12 for the treatment of osteoarthritis.

17. A method according to Claim 13 for the treatment of rheumatoid arthritis..

18. Use of 2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone
in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

~~20.~~ Use according to Claim 18 of 5, 10 or 25mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a

medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

21. Use according to Claim 18 of 10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

22. Use according to Claim 18 of 10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

23. Use according to Claim 18 of 10, 25 or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

24. Use according to Claim 18 of 10, 25 or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of osteoarthritis.

25. Use according to Claim 18 of 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

26. Use according to Claim 18 of 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-

furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of rheumatoid arthritis.

27. Use according to Claim 18 of 5, 10 or 25mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of non-chronic headache, pain or swelling.

28. A unit dose oral form which comprises from 5 to 22.5 mg of dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

29. A unit dosage form according to Claim 28 which comprises 12.5 or 20 mg of dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/34
US CL :514/473

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/473

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
search terms: cyclooxygenase, furanone, inflammation, antiinflammatory, headache, pain, osteoarthritis, arthritis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,474,995 A (DUCHARME ET AL) 12 December 1995, column 1, lines 54-56; column 6, line 16; column 63, example 12.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
16 JULY 1997	12 AUG 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer WILLIAM JARVIS Telephone No. (703) 308-1235

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